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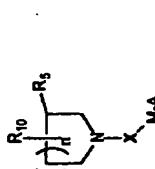
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(57) Abstract
Orally-active nipecotamide-glycolamide ester derivatives of formula (1) are disclosed as useful in treating platelet-mediated thrombotic disorders.

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**ORALLY-ACTIVE NIPECOTAMIDE GLYCOLAMIDE ESTERS FOR THE
TREATMENT OF THROMBOSIS DISORDERS**

CROSS-REFERENCE TO RELATED APPLICATION

This application claims priority from U.S. Serial No. 60/063366, filed October 29, 1997, the contents of which are hereby incorporated by reference.

BACKGROUND OF THE INVENTION

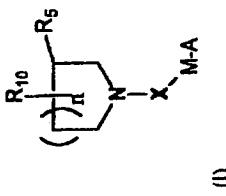
Platelet aggregation constitutes the initial hemostatic response to curtail bleeding induced by vascular injury. However, pathological extension of this normal hemostatic process can lead to thrombus formation. The final, common pathway in platelet aggregation is the binding of fibrinogen to activated, exposed platelet glycoprotein IIb/IIIa (GPIIb/IIIa). Agents which interrupt binding of fibrinogen to GPIIb/IIIa, therefore, inhibit platelet aggregation. These agents are, therefore, useful in treating platelet-mediated thrombotic disorders such as arterial and venous thrombosis, acute myocardial infarction, unstable angina, reocclusion following thrombolytic therapy and angioplasty, inflammation, and a variety of vaso-occlusive disorders. The fibrinogen receptor (GPIIb/IIIa) is activated by stimuli such as ADP, collagen, and thrombin exposing binding domains to two different peptide regions of fibrinogen: alpha-chain Arg-Gly-Asp (RGD) and gamma-chain His-His-Leu-Gly-Gly-Ala-Lys-Gln-Ala-Gly-Asp-Val (HHLGGAKQAGDV, 1400-411). Since these peptide fragments themselves have been shown to inhibit fibrinogen binding to GPIIb/IIIa, a mimetic of these fragments would also serve as an antagonist. In fact, prior to this invention, potent RGD-based antagonists have been revealed which inhibit both fibrinogen binding to GPIIb/IIIa and platelet aggregation e.g., Ro-438857 (L. Alig, *J. Med. Chem.* 1992, 35, 4393) has an IC₅₀ of 0.094 μ M against *in vitro* thrombin-induced platelet aggregation. Some of these agents have also shown *in vivo* efficacy as antithrombotic agents and, in some cases, have been used in conjunction with fibrinolytic therapy e.g., t-PA or streptokinase, as well (J. A. Zablocki, *Current Pharmaceutical Design* 1995, 1, 533).

The glycolamide ester compounds of the present invention are orally-active GPIIb/IIIa antagonists which exhibit improved oral absorption and in vivo activity over their carboxylic acid congeners. As demonstrated by the results of the pharmacological studies described hereinafter, the compounds show the ability to block fibrinogen binding to isolated GPIIb/IIIa (IC₅₀'s of ca. 0.0005-0.01 μ M), inhibit platelet aggregation *in vitro* in the presence of a variety of platelet stimuli (IC₅₀'s of ca. 0.1-1.0 μ M vs. thrombin), and

10 Additionally, these agents exhibit efficacy in animal thrombosis models as their progenitors had shown ("Nipecolic Acid Derivatives As Antithrombotic Compounds," application Serial No. 08-213772, filed March 16, 1994 and "Carboxamide Derivatives of Pyridine, Piperidine, and Hexahydroazepine for the Treatment of Thrombosis Disorders," application Serial No. 60-016875, filed May 1, 1996). The compounds of the present invention are carboxylic acid glycolamide esters which show efficacy as antithrombotic agents by virtue of their ability to prevent platelet aggregation. Additionally, because the compounds of this invention inhibit integrin-mediated cell-cell or cell-matrix adhesion, they may be useful against inflammation, bone resorption, tumor metastasis etc. (1) *Cox Drug News & Perspectives* 1995, A 197

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The present invention is directed to compounds represented by the following general formula (IV):



wherein A, X, M, R5, R10, and n are as hereinafter defined. The glycolamid ester compounds of the present invention are orally-active GPIIb/IIIa antagonists which exhibit improved oral absorption and in vivo activity over their carboxylic acid congeners. These platelet aggregation inhibitors are useful in treating platelet-mediated thrombotic disorders such as arterial and

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wherein A, X, M, R5, R10, and n are as hereinafter defined. The glycolamid

as antithrombotic agents and, in some cases, have been used in conjunction with fibrinolytic therapy e.g., t-PA or streptokinase, as well (J. A. Zablocki, *Current Pharmaceutical Design* 1995, 1, 533).

or the enantiomer or the pharmaceutically acceptable salt thereof.

Preferably, the group $C(O)NR1YZ$ is attached to the ring carbon of the central azacycle at the 3- or 4-position (4-position when larger than a five-membered ring), and most preferably the 3-position.

As used herein, unless otherwise noted alkyl and alkoxy whether used alone or as part of a substituent group, include straight and branched chains having 1-8 carbons. For example, alkyl radicals include methyl, ethyl, propyl, isopropyl, *n*-butyl, isobutyl, *n*-butyl, *n*-pentyl, 3-(2-methyl)butyl, 2-pentyl, 2-(methylbutyl), neopentyl, *n*-hexyl, 2-hexyl and 2-methylpentyl. Alkoxy radicals are oxygen ethers formed from the previously described straight or branched chain alkyl groups. Cycloalkyl groups contain 5-8 ring carbons and preferably 6-7 carbons.

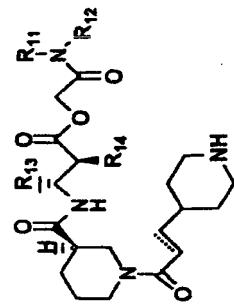
The term "aryl", "heteroaryl" or "substituted heteroaryl" as used herein alone or in combination with other terms indicates aromatic or heteroaromatic groups such as phenyl, naphthyl, pyridyl, thiényl, furanyl, or quinolinyl wherein the substituent is an aryl group. The term "alkaryl" means an alkyl group substituted with an aryl group.

The term "acyl" as used herein means an organic radical having 2-6 carbon atoms derived from an organic acid by removal of the hydroxyl group.

The compounds of the present invention may also be present in the form of a pharmaceutically acceptable salt. The pharmaceutically acceptable salt generally takes a form in which the nitrogen on the 1-piperidine (pyrrolidine, piperazine) substituent is protonated with an inorganic or organic acid. Representative organic or inorganic acids include hydrochloric, hydrobromic, hydroiodic, perchloric, sulfuric, nitric, phosphoric, acetic, propionic, glycolic, lactic, succinic, maleic, fumaric, malic, tartaric, citric, benzic, mandelic, methanesulfonic, hydroxyethanesulfonic, benzenesulfonic, oxalic, pamoic, 2-naphthalenesulfonic, *p*-toluenesulfonic, cyclohexanesulfamic, salicylic, saccharinic or trifluoroacetic acid.

Particularly preferred compounds of the present invention include those compounds shown in Table 1. Where it is noted, the letter "R" indicates the absolute configuration (Cahn-Ingold-Prelog rules).

TABLE I



	#	R ₁₃	R ₁₄	R ₁₁ /R ₁₂	R ₁₁ /R ₁₂
5	1	3-Pyridyl	3,4-OCH ₂ OPh	Et	H
	2	5-Bromo-3-pyridyl	H	Et	H
	10	4	H	Et	NHCO ₂ CH ₂ Ph
	5*	H	H	Et	NHCO ₂ CH ₂ Ph
	6*	H	(CH ₂) ₅	(CH ₂) ₅	NHCO ₂ CH ₂ Ph
15	15	* Compound contains 4-piperidine-3-propenoyl N-terminus (compounds #1-4 contain 4-piperidine-3-propanoyl N-terminus).			

* Compound contains 4-piperidine-3-propenoyl N-terminus (compounds #1-4 contain 4-piperidine-3-propanoyl N-terminus).

The compounds of the invention wherein R₁₀ is H, R₅ is C(O)NHQ(CHW)CO₂R₃, and A is piperidin-4-yl, may be prepared as shown in Schemes AA and AB. Enantiomerically-enriched R-(+)-Hippocrotic acid ethyl ester was isolated by chiral resolution of racemic material as its corresponding D-tartaric acid salt (A. M. Akkerman, *Rec. Trav. Chim. Pays-Bas* 1951, 70, 899), and then converted to Boc-R-hippocrotic acid using standard conditions (aq. sodium hydroxide, di-*t*-butyldicarbonate). Intermediate AA1 was prepared as detailed in provisional U.S. patent application 60-016675 (May 1, 1996) and as published (J. Rico, *J. Org. Chem.* 1993, 58, 7949). Standard amide bond coupling conditions using AA1, HBTU, HOBT, and Boc-R-hippocrotic acid, followed by Boc removal with HCl afforded AA2. Compound AA2 was then acylated with HBTU-activated Boc-4-piperidinepropanoic acid and the resultant methyl ester saponified with lithium hydroxide to give acid AA3. The carboxylate AA3 was then alkylated

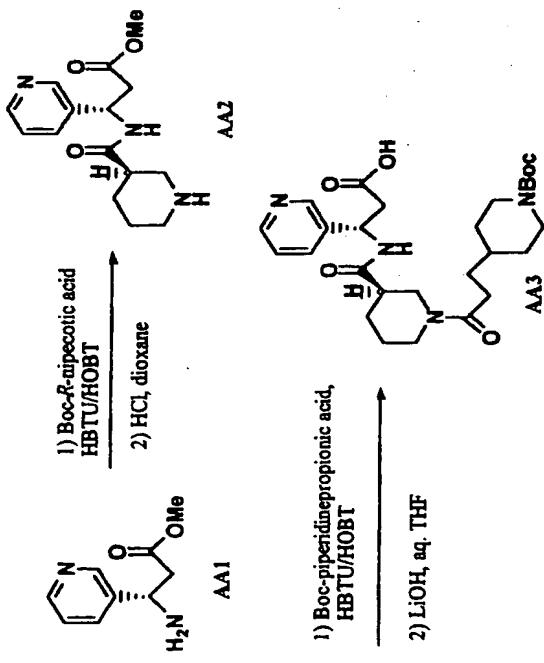
with 2-chloro-*N,N*-diethylacetamide/triethylamine in *Et*OAc, and the Boc group removed with HCl to give final product #1 as its dihydrochloride salt. Compounds #2 and #3 were prepared as shown for #1, resolved β -amino ester starting materials (see AA1 experimental) were prepared as shown for

5 AA1.

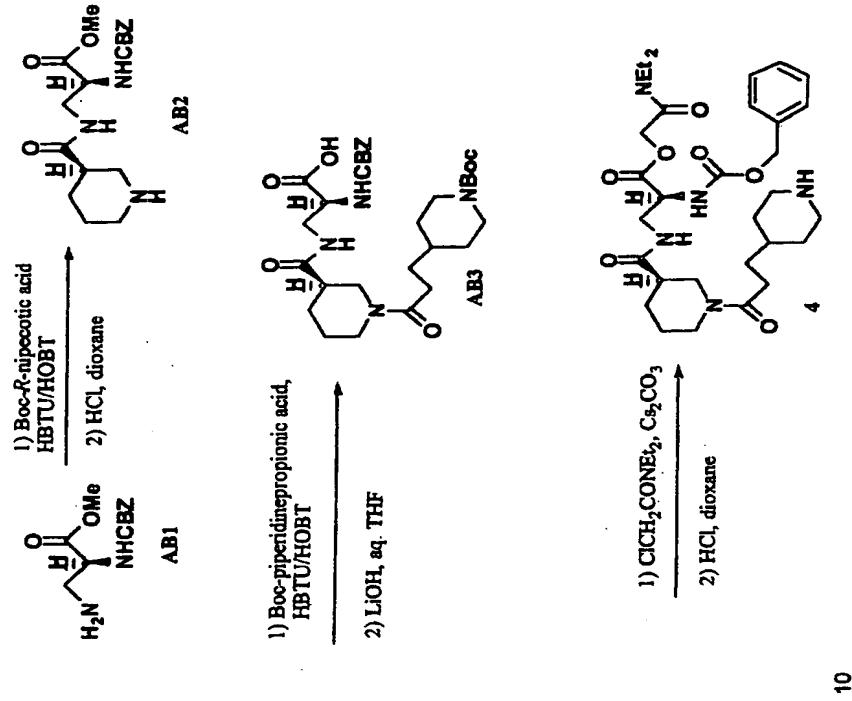
diaminopropionic acid) and then the Boc group removed with HCl to afford AB2. In this synthetic sequence, acid AB3 was alkylated using 2-chloro-*N,N*-diethylacetamide/caesium carbonate in DMF, and then converted to #4 with HCl.

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SCHEME AA



SCHEME AB

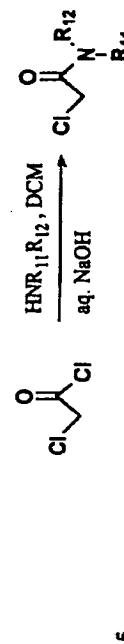


10 Compound #4 was prepared in a similar manner. Boc-R-ripecotic acid was coupled with methyl N - α -CBZ-L-diaminopropionate (prepared by *M*MeOH/HCl Fischer esterification of commercially-available N - α -CBZ-L-

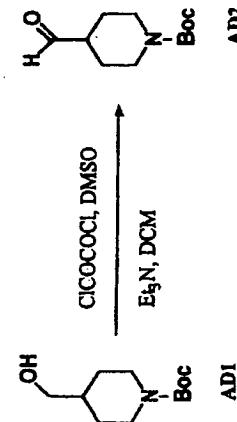
2-chloro-*N,N*-diethylacetamide was purchased from Aldrich Chemical Company. Chloroacetamides may be prepared in one step from 2-chloroacetyl chloride and the appropriate amine (Scheme AC; K. Krakowiak, 15 *J. Heterocyclic Chem.* 1989, 26, 661.). In this procedure, 2-chloroacetyl

chloride and aq. sodium hydroxide were added dropwise to a solution of amine/DCM at RT and reacted over a 1-2 h period.

SCHEME AC



SCHEME AD



To prepare the compounds where A is piperazin-1-yl, intermediate AA2 was acylated with acryloyl chloride/NMM as published (S. G. Gilbreath, *J. Am. Chem. Soc.* 1988, 110, 6172), and the corresponding acylamide then treated with the appropriate piperazine (e.g. N-methylpiperazine) in refluxing ethanol to give the piperazine product.

15 To prepare the compounds where A is piperazin-1-yl, intermediate AA2 was acylated with aldehyde/sodium cyanoborohydride in ethanol to give the N-alkylpiperidine. Formamidinopiperidines were prepared by treating compound #1, for example, with ethyl formimidate-HCl in ethanol; the corresponding acetamidinopiperidines were prepared using S-2-naphthylmethyl thioacetimidate-HCl in ethanol (B. Shearer, *Tetrahedron Lett.* 1997, 38, 179).

20 To prepare the compounds where A is NH₂, intermediate AA2 was acylated with N-Boc-R₂-aminohexanoic acid, for example, using the standard HBTU coupling conditions cited for example 1.

25 Compounds where M is ethynyl were prepared by displacement of N-Boc-4-methanesulfonyloxy(piperidine with potassium ethyl propiolate (potassium carbonate/ethyl propiolate) to give methyl N-Boc-4-piperidinoprop-3-ynoate (T. Jeffery, *Tetrahedron Lett.* 1989, 30, 2225). This ester was then saponified to the corresponding carboxylic acid and coupled with intermediate AA2 using HBTU.

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10 Intermediate N-Boc-4-piperidinopropenoic acid AD3 may be prepared as shown in Scheme AD. Alcohol AD1 was oxidized to the corresponding aldehyde AD2 using standard Swern conditions (oxalyl chloride/DMSO). AD2 was converted to the olefinic ester using the Wittig reagent in dichloromethane. This ester was then saponified to the acid in sodium hydroxide to afford AD3. To prepare compound #5, AD3 was coupled with AB2 as described for compound #4 (HBTU/HOBt) and carried forward to final product as shown in Scheme AB.

Compounds where R₁₀ is C(O)NR(1)YZ and R₅ is H are prepared according to the method described in Scheme AA using an appropriately substituted boc-R-nipeptic acid as the starting material.

5 To prepare the pharmaceutical compositions of this invention, one or more compounds of formula (I) or salt thereof of the invention as the active ingredient, is intimately admixed with a pharmaceutical carrier according to conventional pharmaceutical compounding techniques, which carrier may take a wide variety of forms depending of the form of preparation desired for administration, e.g., oral or parenteral such as intramuscular. In preparing the compositions in oral dosage form, any of the usual pharmaceutical media may be employed. Thus, for liquid oral preparations, such as for example, suspensions, elixirs and solutions, suitable carriers and additives include water, glycols, oils, alcohols, flavoring agents, preservatives, coloring agents and the like; for solid oral preparations such as, for example, powders, capsules, caplets, gelcaps and tablets, suitable carriers and additives include starches, sugars, diluents, granulating agents, lubricants, binders, disintegrating agents and the like. Because of their ease in administration, tablets and capsules represent the most advantageous oral dosage unit form, in which case solid pharmaceutical carriers are obviously employed. If desired, tablets may be sugar coated or enteric coated by standard techniques. For parenterals, the carrier will usually comprise sterile water, through other ingredients, for example, for purposes such as aiding solubility or for preservation, may be included. Injectable suspensions may also be prepared, in which case appropriate liquid carriers, suspending agents and the like may be employed. The pharmaceutical compositions herein will contain, per dosage unit, e.g., tablet, capsule, powder, injection, teaspoonful and the like, an amount of the active ingredient necessary to deliver an effective dose as described above. The pharmaceutical compositions herein will contain, per unit dosage unit, e.g., tablet, capsule, powder, injection, suppository, teaspoonful and the like, of from about 0.03 mg to 100 mg/kg (preferred 0.1-30 mg/kg) and may be given at a dosage of from about 0.1-300 mg/kg/day (preferred 1-50 mg/kg/day). The dosages, however, may be varied depending upon the requirement of the patients, the severity of the condition being treated and the compound being employed. The use of either daily administration or post-periodic dosing may be employed.

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BIOLOGY

The glycolamide ester compounds of the present invention are orally-active GPIIb/IIIa antagonists which show improved oral absorption and in vivo activity over their carboxylic acid congeners. For instance, compound #4 exhibited >240 min duration in vivo (see Table III) whereas its carboxylic acid congener exhibited 180 min duration at the same oral dose. The compounds interrupt binding of fibrinogen to platelet glycoprotein IIb/IIIa (GPIIb/IIIa) and thereby inhibit platelet aggregation. Such compounds are, therefore, useful in treating platelet-mediated thrombotic disorders such as arterial and venous thrombosis, acute myocardial infarction, reocclusion following thrombolytic therapy and angioplasty, and a variety of vaso-occlusive disorders. Because the final, common pathway in normal platelet aggregation is the binding of fibrinogen to activated, exposed GPIIb/IIIa, inhibition of this binding represents a plausible antithrombotic approach. The receptor is activated by stimuli such as ADP, collagen, and thrombin, exposing binding domains to two different peptide regions of fibrinogen: α -chain Arg-Gly-Asp (RGD) and γ -chain 400-411. As demonstrated by the results of the pharmacological studies described hereinafter, the compounds of the present invention show the ability to block fibrinogen binding to isolated GPIIb/IIIa (IC₅₀'s 0.0006-0.005 μ M), inhibit platelet aggregation *in vitro* in the presence of a various of platelet stimulii (IC₅₀'s 0.14-1.1 μ M vs. thrombin), and furthermore, inhibit *ex vivo* platelet aggregation in animal models.

5 *IN VITRO SOLID PHASE PURIFIED GLYCOPROTEIN IIb/IIIa BINDING ASSAY.*

A 96 well Immulon-2 microtiter plate (Dynatech-Immulon) is coated with 30 50 μ l/well of RGD-affinity purified GPIIb/IIIa (effective range 0.5-10 μ g/mL) in 10 mM HEPES, 150 mM NaCl, 1 mM at pH 7.4. The plate is covered and incubated overnight at 4°C. The GPIIb/IIIa solution is discarded and 150 μ l of 5% BSA is added and incubated at RT for 1-3 h. The plate is washed extensively with modified Tyrodes buffer. Biotinylated fibrinogen (25 μ l/well) at 2 \times final concentration is added to the wells that contain the test compounds (25 μ l/well). The plate is covered and incubated at RT for 2-4 h. Twenty minutes prior to incubation completion, one drop of Reagent A (Vecta Stain ABC Horse Radish Peroxidase kit, Vector Laboratories, Inc.) and one

drop Reagent B are added with mixing to 5 ml modified Tyrodes buffer mix and let stand. The ligand solution is discarded and the plate washed (5 x 200 μ l/well) with modified Tyrodes buffer. Vecta Stain HRP-Biotin-Avidin reagent (50 μ l/well, as prepared above) is added and incubated at RT for 15 min. The 5 Vecta Stain solution is discarded and the wells washed (5 x 200 μ l/well) with modified Tyrodes buffer. Developing buffer (10 mL of 50 mM citrate/phosphate buffer @ pH 5.3, 6 mg α -phenylenediamine, 6 μ l 30% H₂O₂; 50 μ l/well) is added and incubated at RT for 3-5 min, and then 2N H₂SO₄ (50 μ l/well) is added. The absorbence is read at 490 nM. The results 10 are shown in Tables II.

IN VITRO INHIBITION OF THROMBIN-INDUCED GEL-FILTERED PLATELET AGGREGATION ASSAY.

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The percentage of platelet aggregation is calculated as an increase in light transmission of compound-treated platelet concentrate vs. control-treated platelet concentrate. Human blood is obtained from drug free, normal donors into tubes containing 0.13M sodium citrate. Platelet rich plasma (PRP) is collected by centrifugation of whole blood at 200 x g for 10 min at 25°C. The 20 PRP (5 mL) is gel filtered through Sepharose 2B (bed volume 50 mL), and the platelet count is adjusted to 2×10^7 platelets per sample. The following constituents are added to a siliconized cuvette: concentrated platelet filtrate and Tyrodes buffer (0.14M NaCl, 0.0027M KCl, 0.0027M NaHCO₃, 0.76 mM Na₂HPO₄, 0.0055M glucose, 2 mg/ml BSA and 5.0mM HEPES @ pH 7.4) in an amount equal to 350 μ l, 50 μ l of 20 mM calcium and 50 μ l of the test compound. Aggregation is monitored in a BIODATA aggregometer for the 3 25 min following the addition of agonist (thrombin 50 μ l of 1 unit/mL). The results are shown in Tables II.

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TABLE II
In Vitro Results

5	Compound #	Fibrinogen Binding			Platelet Aggregation*		
		% Inh. (50 μ M)	[C ₅₀ (μ M)]	% Inh. (50 μ M)	[C ₅₀ (μ M)]		
1	1	100%	0.0007	100%	0.14		
2	2	100%	0.005	100%	1.1		
3	3	100%	0.0039	100%	0.19		
4	4	100%	0.0020	100%	0.29		
10	5	100%	0.0097	100%	0.27		
10	6	100%	0.0025	100%	0.51		

* Thrombin-induced aggregation of gel-filtered platelets. NT = not tested.

EX VIVO DOG STUDY

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Adult mongrel dogs (8-13 kg) were anesthetized with sodium pentobarbital (35 mg/kg, i.v.) and artificially respiration. Arterial blood pressure and heart rate were measured using a Millar catheter-tip pressure transducer inserted in a femoral artery. Another Millar transducer was placed in the left ventricle (LV) via a carotid artery to measure LV end diastolic pressure and indices of myocardial contractility. A lead II electrocardiogram was recorded from limb electrodes. Catheters were placed in a femoral artery and vein to sample blood and infuse drugs, respectively. Responses were continuously monitored using a Modular Instruments data acquisition system.

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Arterial blood samples (5-9 ml) were withdrawn into tubes containing 3.8% sodium citrate to prepare platelet rich plasma (PRP) and to determine effects on coagulation parameters: prothrombin time (PT) and activated partial thromboplastin time (APTT). Separate blood samples (1.5 ml) were withdrawn in EDTA to determine hematocrit and cell counts (platelets, RBC's and white cells). Template bleeding times were obtained from the buccal surface using a symplate incision devise and Whatman filter paper.

Aggregation of PRP was performed using a BioData aggregometer.
35 Aggregation of whole blood used a Chronolog impedance aggregometer. PT and APTT were determined on either a BioData or ACL 3000+ coagulation analyser. Cells were counted with a Sysmex K-1000.

Compounds were solubilized in a small volume of dimethylformamide (DMF) and diluted with saline to a final concentration of 10% DMF. Compounds were administered by the intravenous route with a Harvard infusion pump. Doses was administered over a 15 min interval at a constant rate of 0.33 ml/min. Data were obtained after each dose and in 30 min intervals following the end of drug administration. Oral doses were administered as aqueous solutions via syringe.

Compounds caused marked inhibition of ex vivo platelet aggregation responses. Thus, in whole blood, the compounds inhibited collagen-stimulated (or ADP) aggregation in doses of 0.1-10 mg/kg with marked inhibition of collagen stimulated platelet ATP release. In PRP, the compounds also inhibited collagen stimulated platelet aggregation with marked activity at 0.1-10 mg/kg. Compounds had no measurable hemodynamic effect in doses up to 1 mg/kg, iv. The drugs produce an increase in template bleeding time at 0.1-1 mg/kg with rapid recovery post treatment. No effects on coagulation (PT or APTT) were observed during treatment and platelet, white and RBC counts were unchanged at any dose of the compounds.

The results indicate that the compounds are broadly effective inhibitors of platelet aggregation ex vivo (antagonizing both collagen and ADP pathways) following iv administration of doses ranging from 0.3-1.0 mg/kg or 3 mg/kg orally. The antiaggregatory effects are accompanied by increases in bleeding time at the higher doses. No other hemodynamic or hematologic effects are observed. The results are shown in Table III.

TABLE III
Ex Vivo Dog Study Results

	5	Compound #	5	Intravenous Dosing Dose	Duration*	Oral Dosing Dose	Duration*
5	1	1	0.3 mpk	60 min	3 mpk	>180 min	
10	2	2	1.0 mpk	120 min	3 mpk	150 min	
15	3	NT	NT	NT	3 mpk	80 min	
20	4	0.1 mpk	60 min	3 mpk	>240 min		
25	5	0.1 mpk	60 min	1 mpk	>240 min		
30	6	NT	NT	1 mpk	150 min		

* Indicates duration of >50% inhibition of collagen-induced ex vivo platelet aggregation. NT = not tested.

EXAMPLES

Protected amino acids were purchased from Aldrich Chemical or Bachem Bioscience Inc. N- α -CBZ-L-diaminopropionic acid was purchased from Fluka. Enantiomerically-enriched ripecotic acid ethyl ester was isolated by chiral resolution of racemic material as published (A. M. Akkerman, Rec. Trav. Chim. Pays-Bas 1951, 70, 899). All other chemicals were purchased from Aldrich Chemical Company, Inc. High field 1 H NMR spectra were recorded on a Bruker AC-360 spectrometer at 360 MHz, and coupling constants are given in Hz. Melting points were determined on a Mel-Temp II melting point apparatus and are uncorrected. Microanalyses were performed at Robertson Microt Laboratories, Inc., Madison, New Jersey and are expressed in percentage by weight of each element per total molecular weight. In those cases where the product is obtained as a salt, the free base is obtained by methods known to those skilled in the art, e.g. by basic ion exchange purification. Nuclear magnetic resonance (NMR) spectra for hydrogen atoms were measured in the indicated solvent with tetramethylsilane (TMS) as the internal standard on Bruker AM-360 (360 MHz), AM-400 (400 MHz), or AT-300 (300 MHz) spectrometer. The values are expressed in parts per million down field from TMS. The mass spectra

(MS) were determined on a Finnigan 3300 spectrometer (methane), using desorption chemical ionization techniques. Unless otherwise noted, the materials used in the examples were obtained from readily available commercial suppliers or synthesized by standard methods known to anyone skilled in the art of chemical synthesis. The substituent groups, which vary between examples, are hydrogen unless otherwise noted. In the Examples and throughout this application, the following abbreviations have the meanings recited hereinafter.

10 Bn or Bzl = **Benzyl**
 Boc = **1-Butoxycarbonyl**
 BOC-ON = **2-(1-Butoxycarbonyloxyimino)-2-phenylacetonitrile**
 BOP-CI = **Bis(2-oxo-3-oxazolidinyl)phosphinic chloride**
 CBZ = **Benzoyloxycarbonyl**
 15 CP = **Compound**
 DCE = **1,2-Dichloroethane**
 DCM = **Dichloromethane**
 DIC = **Diisopropylcarbodiimide**
 DIEA = **Diisopropylethylamine**
 20 DMAP = **4-Dimethylaminopyridine**
 DMF = **N,N-Dimethylformamide**
 EDC = **Ethyl dimethylaminopropylcarbodiimide**
 EDTA = **Ethylenediaminetetraacetic acid**
 Et₂O = **Diethyl ether**
 25 HBTU = **2-(1H-Benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate**
 HOBT = **Hydroxybenzotriazole**
 i-Pr = **Isopropyl**
 MPK = **milligrams per kilogram**
 30 NMM = **N-Methylmorpholine**
 Nip = **Nipecotyl** (unless noted otherwise, racemic at 3-position)
 NT = **not tested**
 PPT = **precipitate**
 35 PTS = **p-Toluenesulfonic acid**
 RT = **room temperature**
 TFA = **Trifluoroacetic acid**
 Z = **Benzoyloxycarbonyl**

The following examples describe the invention in greater detail and are intended to illustrate the invention, but not to limit it.

Methyl (S)-3-amino-3-(3-pyridyl) propionate • 2HCl (AA1)

A mixture of 3-pyridinecarboxaldehyde (0.47 mol), EtOH (100 mL), NH₄OAc (0.47 mol), and malonic acid (0.70 mol) was heated at reflux for 6 h, cooled, and filtered. The white solid was washed with EtOH and MeOH and dried (E. Profft, *J. Prakt. Chem.* 1985, 30, 18). This solid was dissolved in 2:1 acetone/water (360 mL), treated with triethylamine (0.72 mol) and phenylacetyl chloride (0.36 mol), and stirred for 22 h. The mixture was evaporated and the residue dissolved in water (500 mL) and adjusted to pH 12 (1 N NaOH). The aqueous layer was adjusted to pH 2 (conc. HCl), extracted with Et₂O, and evaporated to a white foam. The foam was purified by silica gel chromatography (10% MeOH/DCM) to give racemic 3-phenylacetamido-3-(3-pyridyl)propionic acid. A solution of this compound (0.22 mol) in water (600 mL) at RT was adjusted to pH 7.5 using KOH (3.0 N) and treated with penicillin amidase (91520 units, Sigma). This mixture was stirred for 47 h, acidified to pH 1 with HCl (conc), and the resultant ppt filtered through Celite. The filtrate was extracted with Et₂O (3x300 mL), concentrated *in vacuo*, and treated with MeOH/conc. NH₄OH (9:1). This product containing 25 solution was purified by silica gel chromatography (eluent DCM/MeOH/NH₄OH, 78:18:4) to give (S)-3-phenylacetamido-3-(3-pyridyl)propionic acid ammonium salt (19.5 g, 58%). This product was treated with HCl (6.0 N, 292 mL), heated at reflux for 5 h, cooled to RT, and extracted with Et₂O (3x200 mL). The aqueous layer was adjusted to pH 12, 30 concentrated *in vacuo*, and the resultant solid triturated with MeOH (2x300 mL). This solution was evaporated to give ca. 14 g sodium salt. This material was treated with MeOH (500 mL), 2,2-dimethoxypropane (44 mL), and HCl (4 N in dioxane, 84 mL), and stirred for 90 h at RT. This mixture was filtered and the filtrate concentrated *in vacuo*. The resultant off-white solid was triturated with Et₂O (2 x 150 mL) and dried to give compound AA1 (16.7 g, 96% ee) as a white, amorphous solid.

EXAMPLE 1

N-3-(4-Piperidinopropionyl)-R-(4-*N*-isopropyl-(S)-3-amino-3-(3-pyridyl)propanoic acid 2-(Diethylamino)-2-oxoethyl ester • 2HCl(1)

5

To a mixture of AA1 • 2HCl (2.0 g, 8.0 mmol), MeCN (120 mL), Boc-R-nipeptic acid (1.8 g), and HOBT (1.1 g) at 5°C was added NMM (2.6 mL) and HBTU (3.5 g). The mixture was stirred for 20 h, diluted with sat'd ammonium chloride (25 mL), and the MeCN evaporated. This mixture was diluted with EtOAc (120 mL) and the layers separated. The organic layer was dried (sodium sulfate) and evaporated to give a tan foam. The foam was dissolved in dioxane (35 mL) and anisole (1 mL), treated with HCl (25 mL, 4 N in dioxane), and stirred at RT for 2.5 h. The resultant mixture was evaporated and the white foam triturated with Et₂O (50 mL) to give 2.8 g AA2. A mixture of compound AA2, MeCN (120 mL), HOBT (1 g), and HBTU (3.3 g) at 5°C was treated with NMM (2.5 mL) and N-Boc-4-piperidinopropionic acid (1.9 g) and stirred for 4.5 h. The reaction was diluted with sat'd ammonium chloride (30 mL), and the MeCN evaporated. This mixture was diluted with EtOAc (120 mL) and the layers separated. The organic layer was dried (sodium sulfate) and evaporated to give a foam. The foam was purified by silica gel chromatography (0.5% NH₄OH/7% EtOH/DCM) to afford a white foam (2.1 g). This foam was dissolved in THF (25 mL), cooled to 5°C, and treated with eq. lithium hydroxide (0.25 g in 35 mL water). The reaction was stirred for 2 h, acidified with citric acid (0.6 g), and extracted with CHCl₃ (3x50 mL). The combined organics were dried (sodium sulfate) and evaporated to afford AA3 as a white foam (1.8 g). Compound AA3 (1.0 g, 1.9 mmol) was dissolved in EtOAc (50 mL) and triethylamine (0.3 mL) and treated with sodium iodide (0.09 g) and then 2-chloro-N,N-diethylacetamide (0.60 mL). This mixture was stirred for 22 h, diluted with sat'd ammonium chloride (30 mL) and EtOAc (100mL), and the layers separated. The organic layer was dried (sodium sulfate) and evaporated to give a foam. The foam was purified by silica gel chromatography (0.5% NH₄OH/8% EtOH/DCM) to afford a glass (0.56 g). The glass was dissolved in dioxane (25 mL) and anisole (0.5 mL), treated with HCl (15 mL, 4 N in dioxane), and stirred at RT for 4 h. The resultant mixture was evaporated and the white foam triturated with Et₂O (50 mL) to give 1 as a white amorphous solid (0.23 g); mp 93-100°C. ¹H NMR (DMSO-⁴D) δ 8.9 (m, 3 H), 8.6 (m, 2 H), 8.5 (t, 1 H), 8.0 (t, 1 H), 5.4 (m, 1 H), 4.7 (s, 2 H), 4.2 (m, 1 H), 3.7 (m, 2 H), 3.1 (m, 1 H), 2.8 (m, 1 H), 2.6 (m, 4 H), 2.3 (m, 3 H), 1.2-2.0 (m, 13 H), 1.1 (t, 3 H), 0.9 (t, 3 H); MS m/e 530 (MH⁺). Anal. calcd. for C₂₈H₄₃N₅O₅ • 2.3 HCl • 1.3 Dioxane (729.68): C, 52.67; H, 7.69; N, 9.59; Cl, 11.18. Found: C, 52.83; H, 7.99; N, 9.02; Cl, 11.53.

EXAMPLE 2

N-3-(4-Piperidinopropionyl)-R-(4-*N*-isopropyl-(S)-3-amino-3-(3-pyridyl)propanoic acid 2-(Diethylamino)-2-oxoethyl ester • HCl(2)

10

Compound 2 was prepared as described in example 1 starting with methyl (S)-3-amino-3-(3,4-methylenedioxypyridinyl)propionate • HCl (2.2 g), and isolated as a white powder (0.70 g); ¹H NMR (CDCl₃) δ 9.2 (m, 1 H), 8.8 (m, 1 H), 8.4 (d, 1 H), 6.8 (m, 3 H), 5.91 (s, 2 H), 5.4 (m, 1 H), 4.8 (m, 2 H), 4.3 (m, 1 H), 3.7 (m, 1 H), 3.1-3.5 (m, 5 H), 2.6-3.0 (m, 4 H), 2.4 (m, 3 H), 1.6-2.0 (m, 7 H), 1.2-1.5 (m, 7 H), 1.1 (q, 3 H), 0.9 (t, 3 H); MS m/e 573 (MH⁺). Anal. calcd. for C₃₀H₄₄N₄O₇ • 1.7 H₂O (775.55): C, 51.73; H, 6.07; N, 7.22; F, 12.49; KF, 1.16. Found: C, 51.75; H, 6.23; N, 7.13; F, 12.35; KF, 1.12.

EXAMPLE 3

N-3-(4-Piperidinopropionyl)-R-(4-*N*-isopropyl-(S)-3-(5-bromo-3-pyridyl)propanoic acid 2-(Diethylamino)-2-oxoethyl ester • 2HCl(3)

25

Compound 3 was prepared as described in example 1 starting with methyl (S)-3-amino-3-(5-bromo-3-pyridinyl)propionate • 2HCl (2.9 g), and isolated as a white foam (0.40 g); mp 63-65°C. ¹H NMR (DMSO-⁴D) δ 8.8 (m, 3 H), 8.55 (s, 1 H), 8.48 (s, 1 H), 8.4 (m, 1 H), 8.0 (m, 1 H), 5.2 (m, 1 H), 4.72 (s, 2 H), 3.9 (m, 1 H), 3.2 (m, 6 H), 2.9 (m, 2 H), 2.7 (m, 2 H), 2.2 (m, 2 H), 1.9 (m, 3 H), 1.2-1.8 (m, 12 H), 1.1 (t, 3 H), 1.0 (t, 3 H); MS m/e 608 and 610 (MH⁺). Anal. calcd. for C₂₈H₄₂BN₅O₅ • 2.1 HCl • 1.0 H₂O • 0.5 Dioxane (747.23): C, 48.22; H, 6.76; N, 9.37; Cl, 9.96. Found: C, 48.01; H, 6.97; N, 9.13; Cl, 10.28.

35

Compound 3 was prepared as described in example 1 starting with methyl (S)-3-amino-3-(5-bromo-3-pyridinyl)propionate • 2HCl (2.9 g), and isolated as a white foam (0.40 g); mp 63-65°C. ¹H NMR (DMSO-⁴D) δ 8.8 (m, 3 H), 8.55 (s, 1 H), 8.48 (s, 1 H), 8.4 (m, 1 H), 8.0 (m, 1 H), 5.2 (m, 1 H), 4.72 (s, 2 H), 3.9 (m, 1 H), 3.2 (m, 6 H), 2.9 (m, 2 H), 2.7 (m, 2 H), 2.2 (m, 2 H), 1.9 (m, 3 H), 1.2-1.8 (m, 12 H), 1.1 (t, 3 H), 1.0 (t, 3 H); MS m/e 608 and 610 (MH⁺). Anal. calcd. for C₂₈H₄₂BN₅O₅ • 2.1 HCl • 1.0 H₂O • 0.5 Dioxane (747.23): C, 48.22; H, 6.76; N, 9.37; Cl, 9.96. Found: C, 48.01; H, 6.97; N, 9.13; Cl, 10.28.

EXAMPLE 4N-3-(4-Piperidinopropionyl)-R4-(nhecotyl)-H-(S)-2-benzylhexylcarbonylamino-3-aminopropionic acid 2-Diethylamino-2-oxethyl ester · HCl (4)

5

To a mixture of AB1 • 2HCl (12.2 g, 42 mmol), MeCN (300 mL), Boc-R-nipeptic acid (9.7 g), and HOBT (5.8 g) at 5°C was added NMM (9.3 mL) and HBTU (15.9 g). The mixture was stirred for 24 h at 5°C, diluted with sat'd ammonium chloride (50 mL), and the MeCN evaporated. This mixture was washed with sat'd sodium bicarbonate (50 mL), dried (magnesium sulfate), evaporated, and purified by silica gel chromatography (1.5% MeOH/DCM) to give a white foam (14.8 g). The foam was dissolved in dioxane (30 mL), treated with HCl (30 mL, 4 N in dioxane), and stirred at RT for 2 h. The resultant mixture was evaporated and the white foam triturated with Et₂O (50 mL) to give AB2 (13 g). A mixture of compound AB2 (6.3 g), MeCN (200 mL), HOBT (2.1 g), and HBTU (5.9 g) at 5°C was treated with NMM (5.2 mL) and N-Boc-4-piperidinopropionic acid (4.0 g) and stirred for 22 h. The reaction was diluted with sat'd ammonium chloride (40 mL), and the MeCN evaporated. This mixture was diluted with EtOAc (120 mL) and the layers separated. The organic layer was washed with sat'd sodium bicarbonate (30 mL), dried (magnesium sulfate), evaporated, and purified by silica gel chromatography (2.5% MeOH/DCM) to give a foam (7.7 g). 2.5 g of this foam was dissolved in THF (15 mL), cooled to 5°C, and treated with aq. lithium hydroxide (0.17 g in 30 mL water). The reaction was stirred for 2.5 h, acidified with acetic acid (1 mL), and extracted with CHCl₃ (3x50 mL). The combined organics were dried (magnesium sulfate) and evaporated to afford AB3 as a white foam (2.1 g). Compound AB3 (1.0 g, 1.9 mmol) was dissolved in DMF (20 mL), water (5 mL), and cesium carbonate (1.0 g), and treated with 2-chloro-N,N-diethylacetamide (2.1 mL). This mixture was heated at 75°C for 22 h, cooled to RT, concentrated *in vacuo*, and diluted with DCM (60 mL). This mixture was washed with water (25 mL), dried (magnesium sulfate), and evaporated to give a foam. The foam was purified by silica gel chromatography (4%MeOH/DCM) to afford a glass (1.6 g). The glass was treated with HCl (10 mL, 4 N in dioxane), and stirred at RT for 1.5 h to give a ppt. The HCl was decanted and the ppt triturated with Et₂O (50 mL) and dried to afford **4** as a white amorphous solid (0.95 g); mp 57-61°C. ¹H NMR (DMSO-*d*₆) δ 8.9 (m, 1 H), 8.6 (m, 1 H), 8.1 (m, 1 H), 7.7 (f, 1 H), 7.3 (m, 5 H), 5.05 (s, 2 H), 4.8 (m, 2 H), 4.2 (m, 1 H), 3.8 (m, 1 H), 3.1-3.4 (m, 6 H), 2.7 (m, 3 H), 2.3 (m, 2 H), 1.2-1.9 (m, 16 H), 1.1 (t, 3 H), 1.0 (t, 3 H); MS m/e 602 (MH⁺). Anal. calcd. for C₃₁H₄₇N₅O₇ • 1.2 HCl • 1.7 H₂O (676.12); C, 55.07; H, 7.69; N, 10.36; Cl, 6.29. Found: C, 54.86; H, 7.72; N, 10.39; Cl, 5.611.

10 To a solution of oxalyl chloride (24.8 mL, 50 mmol) in DCM (200 mL) at -78°C was added DMSO (7.0 mL) dropwise. The mixture was stirred for 30 min, treated with AD1 (8.2 g, 38 mmol), and stirred for 2 h. Triethylamine (31.7 mL) was added dropwise, the mixture was warmed to RT, and the mixture diluted with water (30 mL). The layers were separated; the organic layer was washed with sat'd ammonium chloride (30 mL) and sat'd sodium chloride (30 mL), dried (magnesium sulfate), evaporated, and purified by silica gel chromatography (20% EtOAc/hexane) to give AD2 (7.3 g, 34 mmol) as a white solid. A solution of ethyl 2-(triphenylphosphorylidenyl)acetate (13.1 g, 38 mmol) and DCM (40 mL) at 5°C was treated with AD2 (7.3 g, 34 mmol) as a pentane (50 mL), and triphenylphosphine oxide removed by filtration. The pentane solution was concentrated and the solid purified by silica gel chromatography (10% EtOAc/hexane) to afford a glass (8.4 g). The glass was dissolved in EtOH (60 mL) and this solution treated with water (60 mL) and sodium hydroxide (59 mL, 1.0 N) at RT. The mixture was stirred for 4 h, acidified with citric acid (8 g), and extracted with DCM (3x100 mL). The combined organics were dried (magnesium sulfate) and evaporated to give AD3 (7.5 g) as a white solid. MS m/e 256 (MH⁺).

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EXAMPLE 6N-3-(4-Piperidin-1-oxopropenyl)-R-(1-hexecetyl)-(S)-2-benzoyloxycarbonylamino-3-aminolpropanoic acid 2-(Diethylamino)-2-oxoethyl ester • HCl (5)

5

Intermediate AD3 (8.5 mmol) and intermediate AB2 (8.5 mmol) were coupled using HBTU/HOBt and the product carried forward to give 5 as described in example 4. Compound 5 was isolated as a white powder (1.6 g); mp 42-45°C. MS m/e 600 (M⁺). Anal. calcd. for C₃₁H₄₅N₅O₇ • 1.0 HCl • 2.0 H₂O (672.22); C, 55.39; H, 7.50; N, 10.42; Cl, 5.27. Found: C, 55.62; H, 7.37; N, 10.44; Cl, 5.27.

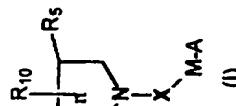
EXAMPLE 6N-3-(4-Piperidin-1-oxopropenyl)-R-(1-hexecetyl)-(S)-2-benzoyloxycarbonylamino-3-aminolpropanoic acid 2-(Piperidin-2-oxethyl) ester • HCl (6)

15

Intermediate AD3 (6.2 mmol) and the piperidine derivative of intermediate AB2 (6.2 mmol) were coupled using HBTU/HOBt and the product carried forward to give 6 as described in example 4. Compound 6 was isolated as a white powder (0.94 g); mp 52-58°C. MS m/e 612 (M⁺). Anal. calcd. for C₂₉H₄₅N₅O₇ • 1.0 HCl • 2.6 H₂O (685.04); C, 55.30; H, 7.42; N, 10.08; Cl, 5.10. Found: C, 55.05; H, 7.39; N, 9.86; Cl, 5.05.

25

1. A compound represented by the general formula (1):



wherein M is (CH₂)_m, CH=CH or C≡C;

10 A is selected from any of piperidin-2-yl, piperidin-3-yl, piperidin-4-yl, piperazin-1-yl, pyrrolidin-2-yl, pyrrolidin-3-yl,



NHR₂ or R₉ wherein R₉ is selected from any of H, alkyl, CH(NH), CMe(NH) or acyl;

15 R10 is H or C(O)N(R₁)YZ,

wherein R1 is selected from H or cycloalkyl;

R2 is selected from any of H, alkyl or acyl;

20 R₅ is H or C(O)NHQ(CHW)-CO₂R₈; wherein Q is selected from CH₂, CH-aryl, CH-heteroaryl, CH-substituted-heteroaryl or CH-alkyl; W is selected from H or N(R₆)T-R₇; wherein R₆ is selected from any of H, alkyl or acyl; T is selected from C(O), C(N-CN) or SO₂; R₇ is selected from any of alkyl, any aralkyl, alkoxy, or aminoalkyl; and R₈ is H or CH₂C(O)NR₁₁R₁₂, wherein R₁₁ and R₁₂ are selected from H, alkyl, or cycloalkyl;

25 m is the integer 1, 2, or 3;

alkoxy, or aminoalkyl; and R8 is H or $\text{CH}_2\text{C}(\text{O})\text{NR}_1\text{R}_2$; wherein R11 and R12 are alkyl;

5 m is the integer 1 or 2;

X is selected from any of C(O), C(O)O, C(O)NH, CH_2 , or SO_2 ;

n is the integer 1, 2, or 3;

10 r is 0 or 1;

Y is selected from any of $(\text{CH}_2)_p$, $\text{CH}(\text{R}3)(\text{CH}_2)_q$, $(\text{CH}_2)_q\text{CH}(\text{R}3)$, $(\text{CH}(\text{CO}_2\text{R}4)\text{CH}_2)_q$, $(\text{CH}_2)_q\text{CHOH}$ or pipericine-3-carboxylic acid; with the proviso that when Y is $(\text{CH}_2)_p$ and p is 2, X is other than C(O) or when X is 15 C(O) then either R1 is other than H or R2 is other than H, and with the proviso that when Y is $(\text{CH}(\text{CO}_2\text{R}4)\text{CH}_2)_q$ X is other than C(O) or CH_2 ;

p is 2 or 3;

20 q is 1;

R3 is alkyl, C₂-C₈ alkenyl, C₂-C₈ alkynyl, aryl, aralkyl or heteroaryl;

R4 is H;

25 Z is $\text{CO}_2\text{CH}_2\text{C}(\text{O})\text{NR}_1\text{R}_2$; provided that at least one of R5 and R10 is hydrogen;

30 provided that when R5 is $\text{C}(\text{O})\text{NHQ}(\text{CH}_2)_p\text{CO}_2\text{R}_8$, and Q is CH-heteroaryl or CH₂-substituted-heteroaryl, and R8 is H, then M is $\text{CH}=\text{CH}_2$; or the enantiomer or the pharmaceutically acceptable salt thereof.

35 7. The compound of claim 6 wherein R8 is $\text{CH}_2\text{C}(\text{O})\text{NR}_1\text{R}_2$,

N-3-(4-Piperidinopropionyl)-R-($\text{--}(\text{S})\text{--}$)-nepicetyl-[(S)-3-amino-3-(3-pyridyl)] propionic acid 2-(Diethylamino)-2-oxoethyl ester • 2HCl,

25

13. The compound of claim 1, selected from any of:

N-3-(4-Piperidinopropionyl)-R-($\text{--}(\text{S})\text{--}$)-nepicetyl-[(S)-3-amino-3-(3-pyridyl)]

N-3-(4-Piperidinopropionyl)-R(-)-nipecoyl-[{(S)-3-amino-3-(3,4-methylenedioxophenyl)} propionic acid 2-(Diethylamino)-2-oxoethyl ester • 2HCl,

5

N-3-(4-Piperidinopropionyl)-R(-)-nipecoyl-[{(S)-3-amino-3-(5-bromo-3-pyridyl)} propionic acid 2-(Diethylamino)-2-oxoethyl ester • 2HCl,

10

N-3-(4-Piperidinopropionyl)-R(-)-nipecoyl-[{(S)-2-benzyl oxy carbonylamino-3-aminol} propionic acid 2-(Diethylamino)-2-oxoethyl ester • HCl,

15

N-t-Butoxy carbonyl-4-piperidine-3-propenoic acid,

N-3-(4-Piperidinopropenoyl)-R(-)-nipecoyl-[{(S)-2-benzyl oxy carbonylamino-3-aminol} propionic acid 2-(Diethylamino)-2-oxoethyl ester • HCl, and

20

N-3-(4-Piperidinopropenoyl)-R(-)-nipecoyl-[{(S)-2-benzyl oxy carbonylamino-3-aminol} propionic acid 2-(Piperidino)-2-oxoethyl ester • HCl.

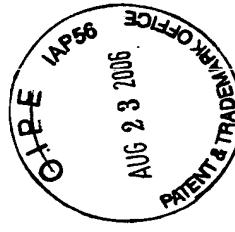
20 14. The compound of claim 1 which is:

N-3-(4-Piperidinopropionyl)-R(-)-nipecoyl-[{(S)-3-amino-3-(3-pyridyl)} propionic acid 2-(Diethylamino)-2-oxoethyl ester.

25 15. A composition for treating platelet-mediated thrombic disorders comprising the compound of Claim 1 in an effective amount for treating such disorders in combination with a pharmaceutically acceptable carrier.

30 16. A method of making the composition of Claim 15 comprising mixing an effective amount of the compound with a pharmaceutically acceptable carrier.

35 17. A method of treating platelet-mediated thrombic disorders comprising administering to a patient afflicted with such disorder an effective amount of the compound of Claim 1 to treat such disorder.



18. The method of Claim 17, wherein the amount is 0.1-300 mg/kg/day.

19. A method of treating platelet-mediated thrombic disorders comprising administering to a patient afflicted with such disorder an effective amount of the composition of Claim 15 to treat such disorder.

20. A method of inhibiting platelet aggregation in a patient in need thereof comprising administering to the patient an effective amount of the compound of Claim 1.

21. The method of Claim 20, wherein the amount is 0.1-300 mg/kg/day.

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